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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	3

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/807,722	Applicant(s) DANIELL, HENRY	
	Examiner Anne Kubelik	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12,14-17,19-28 and 30 is/are rejected.

7)☒ Claim(s) 13 and 29 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are presented, they must be numbered consecutively. There were two claims 14 in the originally filed application. Misnumbered claims 14 (the second)-29 have been renumbered 15-30. Claims 1-30 are pending.

2. The draftsman has approved the drawings as submitted.

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

4. The filing date of one of the provisional applications to which the instant application claims priority is incorrectly indicated in the declaration and the first paragraph of the specification. The provisional application is 60,208,763; it is incorrectly indicated as having a filing date of 6/6/2000, when the correct filing date is 6/2/2000. Correction is required.

Claim Objections

5. Claims 13, 18 and 29 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

6. Claims 4-6, 8, 10, 14-17, 22-28 and 30 are objected to for the following informalities:

Claims 4-6, 8, 14-17, 23-28 and 30 have an improper article at the start of the claim.

Claim 6 lacks an article before "plastid".

Claims 8 and 22 have the misspelling "bytyraldehyde".

There is an improper article before "vector" in claim 10 and before "group" in claim 28.

Claim 25 has a period in the middle of the claim.

In claim 27, "Coli" should not be capitalized.

In claim 30, "5'UTR" should be replaced with --5' UTR--.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-12, 14-17, 19-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plastid transformation vector encoding spinach betaine aldehyde dehydrogenase (BADH) and tobacco plants transformed with it, does not reasonably provide enablement for plastid transformation vector for transforming all plant species, plastid transformation vectors that encode other phytotoxin detoxifying enzymes, plants transformed with these vectors or methods of transforming plant plastids with these vectors or methods of transforming plants other than tobacco. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a multitude of plastid vectors that comprise an expression cassette comprising a 5' part of a plastid sequence inclusive of a spacer sequence, a plastid promoter, a DNA sequence encoding an enzyme that detoxifies phytotoxins, a restriction site, a plastid transcription termination region, and a 3 part of a plastid sequence inclusive of a

spacer sequence, plants transformed with the vectors, and a method of using the vector to transform plastids.

The instant specification, however, only provides guidance for a plastid transformation vector, pLD-BADH, which comprises the spinach BADH cDNA taught in the prior art (pg 9-10), testing the BADH gene expression of pLD-BADH in *E. coli* (pg 12-13), transformation of tobacco with pLD-BADH and selection of the plants spectinomycin and betaine aldehyde (pg 13-14 and 17-18), Southern blot analysis to confirm integration of the vector into the chloroplast genome (pg 14-16), and BADH enzyme assays of crude leaf extracts from transgenic plants (pg 16).

The instant specification fails to provide guidance for the sequences of all other nucleic acids encoding detoxifying enzymes and methods of their use in plastid transformation. The specification fails to teach selection of transformed plants in the presence of phytotoxic agents and phytotoxic aldehydes other than betaine aldehyde.

The instant specification also fails to teach transformation of the plastids of any other plant species, including maize, rice, grass, rye, barley, oats, wheat, soybean, peanut, grape, sweet potato, pea, canola, Brassica, tomato or cotton or the plastid transformation vectors for transforming plants other than tobacco that are mentioned (but not described) on pg 10 of the specification.

Heifetz (2000, Biochimie 82:655-666) teaches that reliable and efficient plastid transformation and regeneration of fertile plants with transformed plastids has been limited to tobacco and potato (pg 658, right column, paragraph 2).

As the specification does not describe the transformation of any plant plastid with a gene encoding the any detoxifying enzyme other than BADH or of any plastid other than those of

tobacco, undue trial and error experimentation would be required to screen through the myriad of vectors encompassed by the claims and plants transformed therewith, to identify those with transformed plastids, if such plants are even obtainable.

9. Claims 1-12, 14-17, 19-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of plastid vectors that comprise an expression cassette comprising a 5' part of a plastid sequence inclusive of a spacer sequence, a plastid promoter, a DNA sequence encoding an enzyme that detoxifies phytotoxins, a restriction site, a plastid transcription termination region, and a 3 part of a plastid sequence inclusive of a spacer sequence, plants transformed with the vectors, and a method of using the vector to transform plastids.

In contrast, the specification only describes a tobacco plastid transformation vector that encodes the spinach BADH. Applicant does not describe other DNA molecules encompassed by the claims, including plastid transformation vectors for transformation of plants species other than tobacco or the sequences of all DNAs that encode enzymes that detoxify phytotoxins, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described plastid transformation vectors within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-12, 14-17, 19-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

It is unclear what is means for a vector to be competent for transforming a plastid or chloroplast genome, as in claims 1 and 8-9. Generally, in transformation, the cell (or plastid) is what is competent for transformation.

Claims 1 and 9 lack antecedent basis for the limitations "the plastid genome" in lines 1-2. "the plastid DNA sequence" in lines 3-4 (line 3 in claim 9), "said plastid" in line 4, "the cells" in line 6, and "the 3' part of a plastid sequence" in line 8 (lines 7-8 in claim 9).

It is unclear in claim 1, line 2, claim 8, line 2, and claim 9, line 2, whose growth is inhibited. The plastid genome? A plant?

It is unclear in claim 1, line 3, claim 9, line 3, and claim 19, lines 4-5, to what the phrase "a 5' part of the plastid sequence" refers. It is not clear to which plastid sequence the part is 5'.

It is unclear in claim 1, lines 4 and 8-9, claim 9, lines 4 and 9, and claim 19, lines 5 and 9, what it means to be inclusive of a spacer sequence or what that spacer sequence is.

Claims 1 and 9 are indefinite in their recitation of "which comprises an expression cassette" in lines 2-3. It appears from the claims that the antibiotic-free phytotoxic agent comprises an expression cassette.

Claims 1 and 19 are indefinite in their recitation of "protein acting as a selectable marker" in lines 5 and 6, respectively. It is unclear under what circumstances the protein does this acting. Proteins do not normally act as selectable markers.

It is unclear in claim 1, line 7, what a "heterologous target gene" means. In what manner is the gene a target? To what is it heterologous?

It is unclear in claim 1, line 8, claim 9, lines 7-8, and claim 19, line 9, to what the phrase "the 3' part of the plastid sequence" refers. It is not clear to which plastid sequence the part is 3'.

Claim 2 lacks antecedent basis for the limitation "one of the restriction sites" in line 2.

It is unclear in the vector of claim 3, where the ribosome binding site and the 5' untranslated region are relative to the other components of the vector.

In claim 8 the phrase "competent for stably transforming the chloroplast genome" is awkward, as a similar phrase is also used to describe the vector of the parent claim. If applicant wishes to limit the plastids of the parent claim to chloroplasts, such a limitation should be explicitly stated. Additionally, the claim lacks antecedent basis for the limitation "the chloroplast genome".

It is not clear in claim 8 whose growth is inhibited by a phytotoxic agent. The chloroplast genome? The vector? How do chloroplast genomes and vectors grow?

Claim 10 is indefinite in its recitation of "the progeny thereof". Does this refer to progeny of the vectors of claim 8 or 9? The chloroplast? The plant?

In claims 11-12, the phrase "edible for a mammal" is awkward and confusing. Additionally, a mammal is able to eat any plant.

Claims 14-15 are not written in proper Markush format. The claims should be in the format "selected from the group consisting of A, B, C and D." In claims 14-15, the comma before "selected" should deleted, --consisting--should be inserted after "group", and "or" should be replaced with --and--. See MPEP § 2173.05(h).

In claim 16, the word --plant-- needs to added onto the end of the claim (so the claim reads "wherein the plant is a tobacco, ... or soybean plant.")

In claim 21, it is unclear how an antibiotic-free phytotoxic agent can code for a phytotoxic aldehyde. Generally, only DNA or RNA codes for something, and neither can code for a phytotoxic aldehyde.

In claim 22, "which" in line 1 should be deleted.

In claims 26-27 it is unclear which DNA sequence is being referred to. The 5' part of a plastid DNA sequence? A DNA sequence encoding a detoxifying enzyme? The heterologous target DNA sequence? The 3' part of the plastid DNA sequence?

Regarding claims 26-27, the phrase "such as" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). In claim 26, its is also unclear if the sequence is from more than one plant, and if this means it is a sequence present in both plants or if it is some sort of hybrid sequence.

Claim 28 not written in proper Markush format. The claims should be in the format "selected from the group consisting of A, B, C and D." The "a" before "group should be replaced with --the--. Additionally, all members of the groups should be singular because "promoter" in line 1 is singular. As written, it appears that there are many of each type of promoter. See MPEP § 2173.05(h).

In claim 30 it is not clear where the rbs and the 5' UTR are located in relationship to the other components of the expression cassette. It is also unclear what it is whose expression is enhanced.

12. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claims is an omnibus type claim.

13. Claims 19-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The method is one of transforming the plastid genome of a plant cell, but the only step is one of introducing into cells (which should be a cell) an expression cassette. The omitted step is transformation of the plastid. Dependent claims are included in the rejection.

14. Claims 23-27 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The method requires culturing a plant. However, the method of the parent claim only involves introducing an expression cassette into a cell. The omitted step is regenerating the cell into a plant. Dependent claims are included in the rejection.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-12, 14-17, 19-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al (1999, US Patent 5,877,402) in view of Rathinasabapathi et al (1994, Planta 193:155-162).

The claims are drawn to method of plant plastid transformation using a BADH gene as a selectable marker, vectors for use in that method, and plants thereby produced.

Maliga et al disclose plastid transformation vectors comprising the plastid *psbA*, *rps16* or

Prrn promoters and a 5' UTR operably linked to the *aadA* or *uidA* genes, the 3' region of the plastid *psbA*, *rps16*, *rbcL* genes, a multicloning site, and flanking DNA sequences for targeting to the plastid genome (the *rbcL* sequence and the ORF512 sequence, or the *rps12* sequence and the 16S rDNA sequence) (Figures 19C-G, 20C-F, and 22A-C; column 56, line 1-56; column 61, line 55, to column 63, line 16). Maliga et al also disclose plastid transformation vectors that comprise the *Prrn* promoter operably linked a kanamycin resistance gene, the 3' region of the plastid *psbA* gene, and flanking DNA sequences (Figures 8 and 9E; column 38, line 25, to column 43, line 47). The vectors of Maliga et al also have a ribosome binding site (claims 16 and 24). Maliga et al do not disclose the use of the BADH gene as a selectable marker.

Rathinasabapathi et al teach transformation of tobacco plants with a spinach or beet gene encoding BADH (pg 157). The protein is targeted to the chloroplasts (pg 157-158) and the resulting plants are resistant to betaine aldehyde (pg 159-160).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of transforming plant plastids as taught by Maliga et al to use the BADH gene as a selectable marker as described in Rathinasabapathi et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Rathinasabapathi et al to use betaine aldehyde resistance as a selectable marker in plants that lack glycine betaine (paragraph spanning the columns, pg 161) and because substitution of chloroplast transformation for chloroplast targeting of a nuclear-encoded gene is an obvious design choice.

17. Claims 1-12, 14-17, 19-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al (*supra*) in view of Ursin (1997, US Patent 5,633,153).

The claims are drawn to method of plant plastid transformation using a BADH gene as a

selectable marker, vectors for use in that method, and plants thereby produced.

Maliga et al disclose plastid transformation vectors and a method of plant plastid transformation, as discussed above. Maliga et al do not disclose the use of the BADH gene as a selectable marker.

Ursin teaches a method of transformation of a variety of plants with spinach, beet or *E. coli* genes encoding BADH (column 7, lines 20-55; claims 1-21). The protein is targeted to the chloroplasts (column 5, lines 17-41) and the resulting plants are resistant to betaine aldehyde (column 10, lines 1-27).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of transforming plant plastids as taught by Maliga et al, and to use the BADH gene as a selectable marker as described in Ursin. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Ursin to use betaine aldehyde resistance as a selectable marker (column 2, line 27, to column 5, line 16) and because substitution of chloroplast transformation for chloroplast targeting of a nuclear-encoded gene is an obvious design choice.

18. Claims 1-12, 14-17, 19-25, 27-28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al (*supra*) in view of Holmstrom et al (1994, Plant J. 6:749-758).

The claims are drawn to method of plant plastid transformation using a BADH gene as a selectable marker, vectors for use in that method, and plants thereby produced.

Maliga et al disclose method of plant plastid transformation, as discussed above. Maliga et al do not disclose the use of the BADH gene as a selectable marker.

Holmstrom et al teach transformation of tobacco plants with an *E. coli* gene encoding

BADH (pg 751). The protein is targeted to the chloroplasts (pg 751-753) and the resulting plants are resistant to betaine aldehyde (pg 753).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of transforming plant plastids as taught by Maliga et al, and to use the BADH gene as a selectable marker as described in Holmstrom et al. One of ordinary skill in the art would have been motivated to do so because substitution of chloroplast transformation for chloroplast targeting of a nuclear-encoded gene is an obvious design choice.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
June 28, 2002

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